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Deep Brain Stimulation

Principal Investigator:
Grant Number: Y1NS200602
Title: Deep Brain Stimulation with VA on Parkinson Disease

Abstract: Unavailable

Principal Investigator: ANDERSON, MARJORIE
Grant Number: 5R01NS044565-03
Title: Deep Brain Stimulation in Parkinson's Models

Abstract: Although high-frequency deep brain stimulation (HF-DBS) in the globus pallidus or subthalamic nucleus has become a common technique used to treat drug-resistant symptoms of Parkinson's disease, the mechanisms by which HF-DBS exerts its effects are unknown. In the proposed studies, the ability of chronic administration of the insecticide rotenone, to produce an animal model of Parkinson's disease will first be tested in monkeys. Using PET imaging now available in the University of Washington Regional Primate Research Center, changes in dopamine innervation after administration of rotenone will be measured using a marker of the monoamine vescicular transporter that is present in dopaminergic nerve terminals. These changes will then be correlated, over time, with changes in behavior and with electrophysiological changes in the rate and pattern of discharge of neurons in basal ganglia-receiving areas of the thalamus. This model will then be used to couple the electrophysiological effects of HF-DBS, which can be recorded from basal ganglia-receiving neurons of the thalamus, to the stimulation-induced changes in regional metabolism in the cortex and thalamus. PET imaging with the metabolic marker, [8-F] flurodeoxyglucose (FDG), will be used to measure metabolism. This technique has generally shown a relative hypermetabolism in the globus pallidus and thalamus of humans with Parkinson's disease and a relative hypometabolism in areas of the frontal cortex. Changes reported to be induced by HF-DBS have been mixed however. The combination of electrophysiology and metabolic imaging will allow us to address some of the discrepancies from the human literature. Special attention will be paid to the development of abnormal patterns of bursting behavior in the thalamus of monkeys treated with rotenone, as well as the effect of HF-DBS on burst behavior. This will test the hypothesis that some of the symptomatology of Parkinson's disease, and its relief using HF-DBS, is a consequence of abnormal patterns of activity in basal ganglia-thalamic-cortical circuits.-

Principal Investigator: ASSAD, JOHN A
Grant Number: 5R01NS041000-05
Title: BASAL GANGLIA FUNCTION--BASIC MECHANISMS AND EFFECTS

Abstract: The basal ganglia (BG) are a set of subcortical nuclei that play a crucial role in the control of voluntary movements. Their importance is underscored by diseases of the BG, such as Parkinson's disease, which compromise the initiation and execution of voluntary movements. While much is known about the general organization of the BG, fundamental questions remain about their role in the normal control of movement. These questions are particularly relevant given the renewed interest in restorative neurosurgical procedures, such as chronic electrical stimulation. that target the BG to relieve Parkinsonian symptoms. The main goal of this is to understand the role of the BG in the normal control of movement, using the awake behaving macaque monkey as an experimental system. The first aim addresses an intriguing paradox about the BG: while diseases affecting the BG cause problems with initiating voluntary movements, most neurophysiological studies have found that neuronal activity in the BG occurs too late to play a role in movement initiation. However, in most of these studies the movements were in response to an external sensory stimulus. There is evidence from Parkinsonian patients that stimulus-cued movements are less severely affected than self-initiated movements. We will thus examine whether the BG play a special role in self-initiated movements - self-initiated with respect to either when a movement is made or which movement is made. The second aim addresses the roles of the direct and indirect BG pathways. The output of the BG is influenced by two distinct pathways with opposing effects on movement: a direct pathway from the striatum which facilitates movement, and an indirect pathway via the subthalamic nucleus (STN) which inhibits movement. While the identification of these pathways has provided a useful framework for understanding movement disorders, many questions remain about their roles in normal movement. We will test one hypothesis, that the two pathways may act in concert to "select" a specific movement among competing possibilities of movement, by examining how neurons in the output nuclei of the BG are affected by electrical inactivation of the STN. For this purpose, it will be necessary to examine the neuronal effects of electrical stimulation in the STN. Little is known about the neuronal effects, even though STN stimulation is now being used to treat Parkinsonian symptoms in human patients. We will directly measure the neuronal effects of electrical stimulation in the STN, and examine how these effects vary with the parameters of stimulation. For this we will develop and test new multielectrode techniques for recording from and

Principal Investigator: CHANG, JING-YU
Grant Number: 5R01NS043441-03
Title: Rat Model of Brain Stimulation in Parkinsonian Condition

Abstract: Deep brain stimulation (DBS) has been used in the clinic to treat Parkinson's disease (PD) during the past decade. The neuronal mechanisms underlying the therapeutic effects of DBS, however, are yet to be clarified. DBS methods have been developed based on the experiments performed exclusively on primate model. Many critical issues regarding the therapeutic effects of DBS need to be addressed using a rodent model. This proposal is aimed at three objectives: first is to establish a rodent model of DBS for Parkinsonian conditions. The rat will be subjected to unilateral 6-hydroxydopamine injection to destroy nigrostriatal dopamine system and thus develop a Parkinsonian motor deficit revealed by treadmill locomotion task. Treadmill will be turned on and off 20 seconds alternatively. Array of ten stimulation electrodes will be implanted in the subthalamic nucleus (STN) and substantia nigra pars reticulata (SNr). High frequency stimulation (HFS) will be applied during the treadmill walking phase. The improvement on locomotion by HFS will be measured and the effects will be compared between STN and SNr stimulations using different stimulation parameters. Second objective is to understand the dynamic neural activity responses in the basal ganglia system during the development of motor deficit by monitoring and comparing the activities from same neurons cross 10 day dopamine depletion period. Chronic multi- channel, single-unit recording technique will be used in this experiment. Sixty-four electrodes will be implanted in the striatum, globus pallidus, STN, and SNr. Extracellular spike activity will be recorded simultaneously in the behavioral rat. This study will test the hypothesis that direct and indirect pathways of basal ganglia will respond in different yet correlated manners during dopamine depletion. Third objective is to study the neuronal mechanisms mediating therapeutic effects of DBS in the behavioral model described above. In addition to the 64 electrodes implanted in the basal ganglia regions mentioned above, eight more stimulation electrodes will be added to target the STN and SNr. The neuronal responses in all four basal ganglia regions during behavioral effective HFS will be recorded and analyzed to reveal the effects of HFS on motor behavioral and associated changes in basal ganglia neuronal activity. This study is designed to address the fundamental mechanisms regarding the effects of DBS on treating PD and the information obtained from this experiment will have direct impact on improving the effects of DBS on PD and other movement disorders.-

Principal Investigator: CHANG, JING-YU
Grant Number: 5R01NS045826-03
Title: Basal Ganglia Neurophysiology during DBS in Rats

Abstract: Parkinson's disease (PD) is a degenerative neurological disorder affecting millions of patients all around the world. Renewed use of the deep brain stimulation (DBS) method provides a new opportunity for treating PD. A key issue to improve the treatment is to fully understand the neural mechanisms underlying the therapeutic effects of DBS. In this proposed study, two unique techniques developed in our laboratory: the chronic multiple-channel single unit recording and rat model of DBS, will be employed to study the neural responses in multiple basal ganglia regions during behaviorally effective DBS in rat model of Parkinsonism. A first objective is to establish a rodent model of DBS in Parkinsonian conditions. The effects of DBS will be evaluated in dopamine lesioned rats performing treadmill locomotion and limb use asymmetry tests. Locomotor d deficits during treadmill walking and imbalance usage of forelimb in vertical exploratory behaviors will develop after unilateral dopamine lesion. High frequency stimulation (HFS) of the subthalamic nucleus (STN) and the substantia nigra pars reticulata (SNr) will then be applied to alleviate these motor abnormalities. The degree of dopamine depletion in the basal ganglia will be detected by immunohistochemical staining of dopamine marker and this result will be correlated with the severity of motor deficits and DBS effects. Second, the basal ganglia neural responses following a dopamine lesion and during behaviorally effective HFS will be examined. Single neural activity and local field potential in the striatum globus pallidus, STN and SNr will be recorded simultaneously in a 64 channel recording system in the rat performing these behavioral tests. Neural responses following dopamine lesion will help us to understand the pathophysiologic process of developing Parkinsonian syndromes while the neural responses during behaviorally effective HFS will shed light on how DBS can restore normal information processing in the basal ganglia neural circuits that are disrupted following dopamine lesion. Several important improvements on recording and stimulation techniques will be made in cooperation with Biographic Inc. to achieve optimal conditions for high frequency stimulation and artifact free recording. The goal of this study is to explore the basic neural mechanism underlying the therapeutic effects of DBS and the knowledge obtained form this study will help us to improve the clinical treatment of PD with DBS method. -

Principal Investigator: Corcos, Daniel M
Grant Number: 5R01NS040902-05
Title: STN STIMULATION--NEURAL CONTROL OF MOVEMENT AND POSTURE

Abstract: High frequency stimulation of the subthalamic nucleus (STN) dramatically improves all of the clinical motor symptoms of Parkinson's Disease (PD). However, there are limited objective data available to determine which characteristics of movement and posture are affected by STN stimulation, and by what neural mechanisms this is accomplished. The long-term objective of this application is to obtain objective neurophysiological data relating to the mechanisms by which effective STN stimulation alters the spatial and temporal patterns of activity mediating planned movement and posture in humans. Patients in whom STN surgery is successful, as defined by a 30% reduction in the motor score of the Unified Parkinson's Disease Rating Scale, will take part in a series of experiments designed to investigate the neural control of movement and posture. The experiments in Aim I will use electromyographic (EMG) and motion analysis techniques to identify which aspects of strength, movement and standing balance are improved, worsened or unchanged by STN stimulation. The effects of STN stimulation will also be compared with the effects of medication on the control of strength and movement. The hypothesis is that neither STN stimulation nor medication normalizes the control of movement, and STN stimulation does not normalize the control of standing balance. Aim 2 will use electroencephalographic (EEG) techniques to test whether STN stimulation-induced changes in movement and gait initiation are accompanied by changes in the spatial and temporal patterns of cortical activity in response to both internally and externally generated cues to move. The hypothesis is that STN stimulation does not normalize the pathways that are normally influenced by the STN but does allow other pathways to compensate better. Aim 3 will combine EEG techniques with stimulation through the quadripolar electrodes implanted in the region of the STN to examine the pathways activated by effective STN stimulation. The findings of the proposed experiments will advance our understanding of the role of the STN in motor function, assist in the development of improved models of the role of the basal ganglia in the control of movement and posture, and thereby contribute to improved treatments for Parkinson's disease. -

Principal Investigator: GISZTER, SIMON F
Grant Number: 5R01NS044564-03
Title: Fiber-Optic Devices for Uncaging of Neurotransmitters

Abstract: The goal of the proposal is to begin to develop and test a tool that can provide focal control of deep neural tissues including excitation, inhibition and modulation state in a fashion compatible with the range of physiological recording techniques. The tool we are designing and testing is a fiber optic light guide system, which is used for focal uncaging of caged neurotransmitters. This system will be coupled with neural recording and neurotransmitter measurement techniques. Such a combined system will allow rapid excitation, inhibition and/or modulation of target tissues, via post-synaptic mechanisms, while introducing no electrical noise for the recording components. There will also be the potential for feedback regulation of activity and of transmitter levels. To test the tool as it is iteratively prototyped we will use several animal models that are well established and understood in our laboratories. Our project has three Specific Aims: 1. Specific Aim 1 Construction and optimization of an implantable fiber optic uncaging system and recording device for use as an experimental tool, in deep brain stimulation and in other neuroprostheses. Specific Aim 2 Development of caged glycine, serotonin and dopamine for experimental and future clinical applications with the fiberoptic system. Specific Aim 3 Validation of developed devices and caged materials in mammalian CNS using physiological and behavioral assays, first in an acute preparation (cat spinal cord), and then in a chronic preparation (rat parabrachial nucleus).-

Principal Investigator: Grill, Warren M.
Grant Number: 7R01NS040894-05
Title: SELECTIVE ELECTRICAL STIMULATION OF THALAMIC NEURONS

Abstract: The primary objectives of the proposed work are to determine what neural elements are activated by DBS, to develop methods to activate selectively local neurons and axons of passage, and to determine the motor effects) of stimulation of different neuronal groups. We will use computer-based modeling of thalamic neurons and the fields generated by DBS electrodes to determine the effects of stimulus parameters and electrode geometry variations on neuronal excitation and block. Hypotheses formulated from computer modeling will be tested. First, using paresthesias evoked by thalamic stimulation in awake human as a unique assay allowing Discrimination of activation of local or remote neural elements, and secondly by quantifying the motor effects:)f selective stimulation of local neurons and axons of passage. The outcomes of this research will be a thorough understanding of what neuronal elements (both type and spatial extent) are affected by DBS and methods to activate selectively targeted populations. We expect to design new stimulus waveforms and electrode geometries that will allow element- and location-specific; st1mulation of the human thalamus. These new techniques will enable us to define the populations of neurons that produce desired and undesired motor effects during DBS, and to specify the next generation of implantable electrodes and stimulators. Collectively, these results will improve the efficacy and expand the range of applications for DBS. Chronic high frequency electrical stimulation of the brain, also called deep brain stimulation,(CBD) is effective in treating a number of neurological disorders, but the mechanisms of action of unclear. A number of plausible hypotheses have been proposed, however, these hypotheses are difficult to support or refute because it is not known what neural elements (local cells, axons of passage) respond at similar stimulation thresholds. This lack of selectivity of the neural response complicates our understanding of the mechanisms of action of DBS, and limits our ability to maximally exploit DBS for therapy. However, if the responsive elements could be controlled selectively, then their differential effects may be used to expand the applications of DBS and minimize undesirable side effects. -

Principal Investigator: JAHANSHAHI, MARJAN
Grant Number: 5R01NS040865-04
Title: DEEP BRAIN STIMULATION--COGNITION/MOTIVATION/MOOD IN PD

Abstract: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has been shown to be an effective treatment for the motor symptoms of Parkinson's disease (PD), particularly improving akinesia and rigidity and reducing levodopa-induced dyskinesias. Neuropsychological investigations have shown that such beneficial effects of DBS on motor function are accompanied by significantly worse performance on specific tests of cognitive executive function such as word fluency and conditional associative learning, respectively when assessed after relative to before surgery or with stimulation on vs off. Surgery for DBS has also been reported to be associated with improvements of depression and anxiety, possibly as a result of the improved motor function, but also some loss of initiative and fatigue suggestive of apathy, a motivational deficit. DBS of the STN is based on current models of fronto-striatal functioning in normals and in PD. The proposed project will involve a more detailed investigation of the impact of DBS on specific tests of executive function (word fluency, random number generation) and learning (conditional associative learning, motor sequence learning) and on mood and motivation using a series of clinical neuropsychological and PET activation studies. The specific aims are: 1.To conduct a number of clinical neuropsychological studies to compare the effects of stimulation on vs off and determine whether DBS results in significant deterioration on tests of cognitive executive function such as word fluency and on tests of learning such as conditional associative learning and motor sequence learning and to clarify the precise nature of the deficits on these tests with stimulation. The impact of DBS on mood and motivation will also be assessed before and 3 months after surgery using a series of standardized questionnaires and interview schedules and the association of these changes to changes in disability and quality of life will also be investigated. 2.To use PET activation studies to identify the mechanisms of change in executive function and learning with DBS of the STN in PD. The effect of stimulation on vs off on regional cerebral blood flow will be measured while patients perform tests of executive function (phonemic word fluency or random number generation), learning (conditional associative learning or motor sequence learning) or matched control tasks and during a choice RT with or without manipulation of motivation (provision of feedback and incentive for fast responses). Any changes in frontal and striatal activation and in fronto-striatal connectivity within and between the motor, associative and limbic circuits will be measured using techniques such as structural equation modeling and regression methods to

Principal Investigator: KELLY, VALERIE E
Grant Number: 1L30NS049916-01
Title: Subthalamic Nucleus Stimulation in Parkinson's

Abstract: Unavailable

Principal Investigator: LARSEN, HUGH G
Grant Number: 5R01NS044554-03
Title: Multichannel Deep Brain Stimulation System

Abstract: This proposal is submitted in response to RFA-NS-02-004 (Technology development for safe and effective deep brain stimulation). We have addressed Research Objective #3, "The development of stimulators that are rechargeable and/or that have a wider range of stimulation rates, stimulation currents, pulse widths, pulse waveforms, and that permit recording from electrodes as well as stimulation." 1) We will develop a stimulator for deep brain stimulation that is rechargeable and that has a wider range of stimulation rates, stimulation currents, and pulse widths than any other available system. This development will include the external recharger and the tools required to program the stimulator. 2) We will develop a stimulator for deep brain stimulation with the above capabilities that can be mounted in the skull, thereby obviating the need to tunnel a lead through the neck. . This allows implantation of the DBS system without the need and the attendant risks of general anesthesia, and this reduces the risk of lead fracture or breakage by avoiding passage of the lead through the highly mobile neck area. 3) We will develop a stimulator for deep brain stimulation that includes sensing of the electrical activity of neurons. This system may use the stimulation electrodes for sensing or may incorporate separate recording electrodes integrated with the stimulation electrode array. The system may also be configured with a connector for a separate recording lead that may be place in a part of the brain that is relatively far removed from the area of stimulation. 4) We plan to make the above stimulators available to members of the NIH Deep Brain Stimulation (DBS) consortium as well as other DBS researchers for research and testing.-

Principal Investigator: MENTIS, MARC J
Grant Number: 5K23NS002204-05
Title: MECHANISMS UNDERLYING THERAPY IN PARKINSON'S DISEASE

Abstract: The award is intended to develop the candidate's research skills in, psychophysics, pharmacology, and advanced functional imaging (systems analysis, and fMRI) to equip him for an independent career evaluating mechanisms underlying successful therapy of cognitive dysfunction in neurodegenerative diseases. Once identified, successful medical and/or surgical mechanisms can be manipulated to refine existing, and develop novel therapies. Research Plan: Parkinson's Disease (PD), expected to afflict 1,000,000 Americans by the year 2000, frequently exhibits cognitive deficits (dysexecutive syndrome) in non- demented PD patients, in addition to the 40% with dementia. While the deficits have been linked to frontal cortical dysfunction and/or a disorder of subcortico-frontal connectivity, the functional basis of these deficits in PD remains poorly understood. Dopamine replacement therapy, successful for the motoric signs of PD, falls to improve the dysexecutive syndrome. Pathological studies show 20% loss of cholinergic cells in subcortical nuclei of non-demented PD patients, abnormal cortical choline acetyltransferase, reduced cortical and subcortical nicotinic receptors, and a correlation between cortical nicotinic loss and cognitive dysfunction. Preliminary clinical reports suggest cognitive improvement with non-specific cholinergic therapy. In Specific Aim 1, the candidate proposes a PET study of PD patients performing kinematically-controlled motor learning and execution tasks at baseline and with cholinergic pharmacotherapy. The pharmacological technique will allow him to identify the contribution of receptor families (muscarinic and/or nicotinic) to cholinergic modulation of specific brain networks known to be associated with learning performance. Based on these results, the candidate will test the hypothesis that nicotinic therapy will improve defined aspects of cognitive dysfunction in PD. The candidate wishes to bridge the gap between clinical of cognitive abnormality, and pathological observation of cholinergic loss, firstly, by quantifying the modulation of cholinergic receptor families on brain networks subserving cognition, then by testing if predicted improvements occur with therapy of a particular receptor family. In Specific Aim 2, the candidate will expand upon a preliminary observation that deep brain stimulation (DBS) may improve learning performance in PD. He will perform a PET study on PD patients on and off subthalamic nucleus (STN) DBS to determine the effect of therapeutic stimulation on the same tasks as in Specific Aim l. This will test the hypothesis that STN DBS may enhance cognitive performance in PD by modulating the expression of subcortico-frontal projection

Principal Investigator: OKUN, MICHAEL S
Grant Number: 5K23NS044997-02
Title: DBS Effects on Mood and Cognition in Parkinsons Disease

Abstract: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) and globus pallidus interna (GPi) has been demonstrated to be effective in the treatment of the cardinal motor symptoms of Parkinson's disease (PD) (tremor, rigidity, and bradykinesia). Both STN and GPi DBS have been documented to be effective in treating parkinsonian motor signs. Due to early limited reports, which suggest more robust improvements in UPDRS motor scores, and the ability to reduce parkinsonian medication with STN, but not GPi, STN has been the preferred target of most centers. There is, however, increasing evidence that STN DBS may be associated with a significant number of mood and cognitive changes. Because of the small size of the STN (158mm3), stimulation within the sensori-motor area can result in spread to limbic and associative areas of STN as well as to surrounding structures and fiber systems that may also affect mood and cognition. Since the Gpi (478mm3) is significantly larger than STN, a lead can be placed in the sensorimotor territory of the GPi with less likelihood of current spread to non-motor portions of the GPi or to adjacent structures and fiber systems that can adversely change mood and cognition. In this proposal we will 1) Characterize and compare the mood and cognitive changes associated with STN and GPi DBS, 2) delineate regions within or around the STN and GPi that are associated with specific mood and cognitive changes during DBS in these regions, and 3) assess the relative effect of right versus left STN or GPi stimulation on mood and cognition. This study will characterize the types and incidence of mood and cognitive changes that occur during stimulation in STN and GPi. It will also compare the relative changes in mood and cognition that occur in each site and examine the role of lead location in mediating them. The research is part of a five-year plan for training and career development for the Principal Investigator. This proposal includes active and experienced mentoring, access to diverse resources, and a scientific environment suited specifically for the development of the PI as an independent physician scientist.-

Principal Investigator: PERLMUTTER, JOEL S
Grant Number: 2R01NS041509-04
Title: MECHANISM OF DEEP BRAIN STIMULATION

Abstract: Deep brain stimulation (DBS) of the subthalamic nuclei (STN) may provide substantial reduction of symptoms in people with Parkinson disease (PD) and DBS of the thalamic ventral intermediate nucleus (VIM) markedly reduces tremor in people with disorders such as essential tremor (ET). Increasing data also indicates that STN DBS in PD may produce unwanted cognitive impairments, such as impairments of spatial delayed recall or response inhibition. Despite these dramatic clinical effects, the precise mechanism of action of DBS remains unclear. Recent studies, including several from this lab, indicate that DBS produces a net increase in neuronal output from the site of stimulation either the STN in PD or VIM in ET, and there may be important differences in the effects of STN on the left and right sides of the brain. Nevertheless, how this action and its asymmetry provide clinical benefit while simultaneously interfering with selected cognitive function remains unknown. We hypothesize that STN and VIM DBS provide motor benefit by altering function of specific motor brain regions, whereas, STN DBS impairs cognitive skills by altering function of selected prefrontal regions. Further, we propose that there are substantial differences between left and right-sided STN stimulation on aspects of motor and cognitive function. We will test these specific hypotheses using PET to measure brain blood flow responses to varying levels of STN or VIM stimulation in people with PD or ET and then correlate these PET responses with cognitive or motor responses to DBS in the same subjects. These studies have the potential to reveal valuable insights into the mechanism of DBS and also into the pathophysiology of these diseases and their clinical manifestations. For example, we may identify specific brain pathways that mediate cognitive impairment from STN DBS that are distinct from those that mediate motor benefit. This could directly lead to designing new strategies to maximize motor benefit and minimize cognitive impairments. We also have the potential to provide a rationale for investigating new sites for DBS that may be more accessible than those currently used. This innovative study brings together rigorous, carefully controlled PET investigations with quantified motor and cognitive behavioral measures.-

Principal Investigator: POIZNER, HOWARD
Grant Number: 2R01NS036449-05A1
Title: Motor Control Deficits in Parkinson's Disease

Abstract: Our findings in the current grant period have led us to hypothesize that a major difficulty for patients with Parkinson disease (PD) is in assembling and using new sensorimotor mappings or coordinations. These process play a major role both in ongoing motor performance and in the acquisition of new skills, in addition, our preliminary data are consistent with a general observation that these processes may be relatively resistant to current therapeutic modalities. Furthering our understanding of this deficit, examining its impact on motor learning, and investigating the ability of dopaminergic therapy to reverse this deficit are the guiding aims of this proposal. The present proposal presents three experiments that are designed to confirm and extend our hypothesis and to investigate the degree to which dopaminergic therapy is able to remediate these deficits. The first two experiments (Specific Aims 1 and 2) introduce the requirement that subjects learn to move within a virtual environment as a prerequisite to establishing the new sensorimotor coordinations necessary for accurate target acquisition. We require subjects to master distortions which create discrepancies between the apparent (virtual) and real (proprioceptively signaled) location of their arms and to generalize the resulting learning to untrained regions of this environment. By dissociating movements from their normal sensory correspondences, we will challenge subjects' abilities to reconfigure their sensorimotor coordinations. The third experiment (Specific Aim 3) challenges patients by requiring them to integrate different motor acts in order to acquire visually-presented, real targets by compensating for a mechanical perturbation of the trunk during a trunk-assisted reach. We have integrated and coupled our previously developed system for analysis and display of three dimensional movements with our newly developed virtual reality environment. We will examine not only subjects' accuracy, but also the path, timing, and structure of their movements under different conditions and types of imposed distortions, in order to measure both performance and learning when PD patients are OFF versus ON dopaminergic therapy. By contrasting the performance and capacities of PD patients on and off dopaminergic therapy to that of comparable normals, we can both obtain clues as to how to overcome PD dysfunction and gain an insight into the key role of the basal ganglia in movement.-

Principal Investigator: REZAI, ALI R
Grant Number: 5R01NS044575-03
Title: Evaluation of MRI Safety for Deep Brain Stimulation

Abstract: There is a growing interest in the use of chronic deep brain stimulation (DBS) of the thalamus, globus pallidus, and the subthalamic nucleus for the treatment of medically refractory movement disorders and other neurological and psychiatric conditions. The number of patients undergoing DBS surgeries is anticipated to increase rapidly. Use of magnetic resonance imaging (MRI) is crucial for the management of patients with DBS. Critical studies include verification of lead position, assessment of patients with poor outcomes, evaluation for other intracranial pathologies, and performing functional MRI studies. However, electronically activated devices are generally considered to be contraindicated for patients undergoing MRI, based on reports of adverse effects in the literature. Our primary hypothesis is that parameters can be defined that will enable safe MR imaging in patients with DBS. Building upon our preliminary data, We intend to conduct a comprehensive safety analysis, functional assessment of the stimulation devices, and evaluation of the artifacts produced by the DBS. We will use 1.5 Tesla and 3Tesla MR systems, body radio frequency (RF) and head RF coils to conduct all experiments. Specifically, in-vitro experiments will be performed to assess DBS magnetic field interactions (translational attraction and torque), MRI-related heating (including computer modeling), induced electrical currents, and identification of any effects on device functionality. The artifacts produced by the DBS electrodes will also be quantified. The identification of safe MRI parameters will enable patients with neurostimulation systems to routinely undergo diagnostic MR procedures and allow the use of this important imaging modality for the optimal localization of DBS electrodes.-

Principal Investigator: TANG, CHA-MIN
Grant Number: 5R01NS044627-03
Title: An Infrared Fiber Optic Based Guidance System for DBS

Abstract: Deep brain stimulation may be used to treat a number of neurological and psychiatric disorders. For treatment in patients with Parkinsons' disease it is necessary to place the electrode precisely within the center of the target nucleus. Precise electrode placement provides optimal therapeutic results while minimizing possible side effects. Currently, the final coordinates for the electrode is determined by electrophysiological mapping. It is a slow, painstaking process not without potential complications. We propose to develop and evaluate two procedures to compliment current microelectrode mapping procedure. A fiberoptic-based probe will be employed to optically map the boundaries of the STN and GPi using only a single electrode tract. We also propose to develop a method to detect blood vessel using fiber sensors as part of the microelectrode assembly. Besides a role in the treatment of Parkinson's disease, the methods to be developed may be applied to stereotactic brain procedures for other neurological and psychiatric disorders. For example, it could be used to more precisely guide the biopsy of deep seated brain lesions. It could be used to more safely guide the placement of depth electrode for the diagnosis and treatment of refractory seizures. And optically guided stimulating electrodes may someday be used to treat depression and other psychological disorders. -

Principal Investigator: TURNER, ROBERT S
Grant Number: 5R01NS044551-03
Title: DBS AND MOTOR CORTICAL FUNCTION IN AN MPTP MODEL OF PD

Abstract: Deep brain stimulation (DBS) of either the internal segment of the globus pallidus (GPO or the subthalamic nucleus (STN) is an effective treatment for most if not all symptoms of Parkinson's disease (PD). Several aspects of the reduction of symptoms with DBS provide tantalizing hints that different symptoms may be mediated by distinct pathways and/or physiological processes involving the motor and premotor cortices. The goals of this project are to use a non-human primate model of PD to gain a better understanding of the cortical mechanisms by which DBS produces clinical benefit, as well as to determine if different symptoms have different neuroanatomic/physiologic substrates. Animals will perform tasks that measure symptom-relevant behavioral parameters: movement selection/initiation/sequencing (akinesia), movement kinematics (bradykinesia), and rigidity. Neuronal activity at multiple locations in the four principal motor cortices [in different animals, primary motor (M1), ventral premotor (PMv), dorsal premotor (PMd), or mesial premotor (SMA)] will be monitored using a multielectrode array. Single cell activity will be assessed for changes in resting firing rate, task-related activity, and cell-to-cell interactions (synchronized firing) in response to DBS in GPI or STN before and after animals are rendered parkinsonian by intracarotid infusion of MPTP. The predictions are that: DBS-related changes in resting discharge will not be correlated with specific changes in symptoms. Increased activity and synchrony in SMA will be associated with reduced akinesia. Increases of the same in M1 will accompany reduced bradykinesia. Reductions in rigidity will be linked with a drop in M1 responses to passive movement and increased directional specificity in movement related activity. In addition, DBS may reduce abnormally-increased activity in PMv and PMd These hypotheses will be tested in three specific aims: Specific aim I will study the interacting effects of DBS and the type of motor task being performed. Specific aims 2 and 3 will identify cortical activities that change in concert with the time course (SA 2) and parametric relations (SA 3, DBS location, frequency, and strength) of symptom reduction with DBS. The results of these experiments will improve understanding of both the neuronal basis of different symptoms of PD and the mechanisms of action of DBS. Ultimately, these studies will advance a more complete pathophysiologic model of PD by incorporating the full array of parkinsonian symptoms.-

Principal Investigator: VAN HORNE, CRAIG G
Grant Number: 1R41NS047959-01
Title: Objective measures of speech post-L-dopa & STN DBS in PD

Abstract: Speech is a complex motor behavior often disrupted by neurologic dysfunction. Parkinson's disease (PD) is one of the most prominent neurological disorders associated with speech disturbances. L-dopa continues to be the cornerstone of medical treatment for the motor symptoms and typically produces some improvement of speech symptoms. As the disease progresses, medical management becomes increasingly difficult and is associated with disabling side effects. Recently, deep brain stimulation (DBS) has been shown to be an effective adjunct therapy for control of the motor symptoms in select patients with advanced disease. The clinical effects of L-dopa and DBS on speech have not been consistent, and some studies report a substantial worsening of speech following these procedures. Many of the difficulties in evaluating speech arise from the subjective nature of evaluation. Even standardized protocols administered by trained professionals demonstrate significant inter-rater variability. We propose to develop a cost effective, portable, stand-alone technology package to analyze multiple components of recorded speech. We will study the applied technology in PD patients and analyze the effects of L-dopa and DBS on objective measures of speech. We will also expand our speech assessment technologies by adding new analytical tools based on sensitive, non-linear dynamic algorithms.-

Principal Investigator: VAWTER, DOROTHY E.
Grant Number: 5R01NS040883-05
Title: ETHICAL AND POLICY CHALLENGES IN THE STUDY AND USE OF DB

Abstract: Unavailable

Principal Investigator: VITEK, JERROLD L
Grant Number: 5R01NS037959-05
Title: DEEP BRAIN STIMULATION FOR PARKINSONS DISEASE

Abstract: The major aim of this study is to carry out a prospective, randomized clinical trial of deep brain stimulation (DBS) in the internal segment of the globus pallidus (GPi) and subthalamic nucleus (STN) for the treatment of advanced Parkinson's disease (PD). Medical therapy is the mainstay of treatment for patients with PD. After several years of drug therapy, however, a large proportion of patients experience worsening of their parkinsonism and develop incapacitating motor fluctuations and dyskinesias. To deal with this, attention has been directed to surgical procedures, especially ablative therapies, e.g. pallidotomy, and more recently deep brain stimulation (DBS). DBS mimics the effects of ablation, but is reversible. It also has the advantage in that one can adjust stimulation parameters to physiologically change the area of inactivation and to implant both sides without the high incidence of complications associated with bilateral pallidotomy. In recent years DBS in the STN and GPi has been explored in pilot studies for the treatment of patients with advanced PD. Only a few nonrandomized studies examining the effect of DBS in the STN and GPi have been performed, however, and the results, although promising, have been highly variable. This study, which follows upon our current NIH supported randomized clinical trial of pallidotomy versus medical management for PD, will comprehensively evaluate the effects of DBS in GPi and STN on motor, neuropsychological and psychiatric function, and quality of life in patients with PD. The current proposal offers the unique opportunity of using the current cohort of patients in the pallidotomy for PD clinical trial for comparison to DBS. This study will address three key issues: 1) whether there are significant differences between GPi-DBS, STN-DBS and GPi pallidotomy. 2) which patients are the best candidates for DBS and 3) whether bilateral stimulation (GPi or STN) is superior to combined GPi pallidotomy and DBS. Overall, these studies will provide important data on the short and long term effects of DBS in the STN and GPi on motor, cognitive and psychiatric functioning and quality of life in parkinsonian patients and provide much needed guidelines regarding patient selection and optimal surgical approach. -

Principal Investigator: VITEK, JERROLD L
Grant Number: 7R01NS037019-06
Title: Deep Brain Stimulation in the Parkinsonian Monkey

Abstract: Over the last decade, the outlook for patients with advanced parkinsonism and other movement disorders has been revolutionized by the introduction of deep brain stimulation (DBS) in the subthalamic nucleus (STN) and internal segment of the globus pallidus (GPi) as a highly effective treatment modality. According to recent estimates over 2000 patients with PD have undergone implantation of DBS electrodes for the treatment of PD and over 15,000 patients per year may be candidates for this procedure. This number will increase, as the use of DBS as treatment of brain disorders becomes more widespread. Despite their widespread use, very little is known about the physiologic effects of DBS. Given the somewhat similar effect of lesions and stimulation in STN, GPI and thalamus on parkinsonian motor signs, it has been speculated that stimulation may act similar to lesioning, by blocking neuronal activity. Several studies have supported this view reporting suppression of neuronal activity in the site of stimulation. Our preliminary results, as well as the results of other groups have suggested that stimulation may, in fact increase output from the stimulated structure, demonstrating that stimulation in the STN increases neuronal activity in the GPi, while GPi stimulation suppresses neuronal activity in the thalamus. Additional support for this hypothesis is derived from microdialysis studies that found increased levels of glutamate in the entopeduncular nucleus (the rodent equivalent of GPi in primates) during STN stimulation. Conceivably, stimulation of basal ganglia activity may improve parkinsonism simply by regularizing pallidal discharge patterns. Both activation and inactivation could, in fact, be invoked during stimulation, because electrical stimulation may inhibit neuronal activity, while activating fibers in the stimulated area. For further optimization of current DBS protocols, and to minimize risks and side-effects of DBS implantation, it is mandatory that a solid understanding of the mechanism of action of this intervention is developed. This study will determine the mechanism underlying the effects of DBS of STN and GPi by examining in the MPTP monkey model of PD: 1) the effect of stimulation in the STN and GPi on neuronal activity and on neurotransmitter release in different portions of the basal ganglia-thalamocortical circuit, 2) the role of GPe in mediating the effect of stimulation in the STN and GPI, in mediating the development of parkinsonian motor signs and as an alternative site for stimulation for the treatment of PD and 3) determine the effect of stimulation in the STN and GPI on cortical function. The experiments will use a combination of single cell recording, microdialysis, and 18F-fluoro-deoxy-glucose

Principal Investigator: VITEK, JERROLD L
Grant Number: 7R01NS037959-06
Title: DEEP BRAIN STIMULATION FOR PARKINSONS DISEASE

Abstract: The major aim of this study is to carry out a prospective, randomized clinical trial of deep brain stimulation (DBS) in the internal segment of the globus pallidus (GPi) and subthalamic nucleus (STN) for the treatment of advanced Parkinson's disease (PD). Medical therapy is the mainstay of treatment for patients with PD. After several years of drug therapy, however, a large proportion of patients experience worsening of their parkinsonism and develop incapacitating motor fluctuations and dyskinesias. To deal with this, attention has been directed to surgical procedures, especially ablative therapies, e.g. pallidotomy, and more recently deep brain stimulation (DBS). DBS mimics the effects of ablation, but is reversible. It also has the advantage in that one can adjust stimulation parameters to physiologically change the area of inactivation and to implant both sides without the high incidence of complications associated with bilateral pallidotomy. In recent years DBS in the STN and GPi has been explored in pilot studies for the treatment of patients with advanced PD. Only a few nonrandomized studies examining the effect of DBS in the STN and GPi have been performed, however, and the results, although promising, have been highly variable. This study, which follows upon our current NIH supported randomized clinical trial of pallidotomy versus medical management for PD, will comprehensively evaluate the effects of DBS in GPi and STN on motor, neuropsychological and psychiatric function, and quality of life in patients with PD. The current proposal offers the unique opportunity of using the current cohort of patients in the pallidotomy for PD clinical trial for comparison to DBS. This study will address three key issues: 1) whether there are significant differences between GPi-DBS, STN-DBS and GPi pallidotomy. 2) which patients are the best candidates for DBS and 3) whether bilateral stimulation (GPi or STN) is superior to combined GPi pallidotomy and DBS. Overall, these studies will provide important data on the short and long term effects of DBS in the STN and GPi on motor, cognitive and psychiatric functioning and quality of life in parkinsonian patients and provide much needed guidelines regarding patient selection and optimal surgical approach. -

Principal Investigator: Walters, Judith
Grant Number: 5Z01NS002139-30
Title: Pharmacology And Physiology Of The Substantia Nigra And Basal Ganglia

Abstract: Unavailable

Principal Investigator: WICHMANN, THOMAS N
Grant Number: 5R01NS040432-04
Title: Influence of subthalamic nucleus on striatal dopamine

Abstract: Degeneration of the dopaminergic nigrostriatal tract results in Parkinson's disease. Over the last years, rodent studies have provided evidence that the activity of the source neurons of the nigrostriatal tract in the substantia nigra pars compacta (SNc) is modulated by afferents from the subthalamic nucleus (STN). Increased STN output, a central feature of most models of parkinsonian pathophysiology, could impact SNc function in early parkinsonism, helping to compensate for the loss of striatal dopamine by increased driving of nigrostriatal neurons. In rodents, STN and SNc are linked via excitatory glutamatergic projections, or via inhibitory pathways involving GABAergic neurons in the substantia nigra pars reticulata (SNr). Activation of the excitatory projections results in increased bursting in SNc, whereas activation of the inhibitory projections lowers the average discharge rates in SNc. Our preliminary data in primates have also demonstrated excitatory and inhibitory effects of STN stimulation on SNc activity, and have indicated that striatal DA levels may be increased with STN stimulation and reduced with STN inactivation. Effects on striatal dopamine may be explained by the direct synaptic STN-SNc interaction, by actions mediated via long loop circuits through thalamus and cortex, as well as by presynaptic mechanisms. The proposed experiments will explore the STN-SNc relationship in primates, with the general hypothesis that STN activation will result in increased burst discharges in SNc and increased dopamine levels in the striatum, while STN inactivation will result in the opposite. A combination of electrophysiologic, microdialysis and anatomic methods will be used to assess effects of transient manipulations of STN activity, induced by intra-STN injections of the GABA receptor agonist muscimol or the GABA receptor antagonist bicuculline, on the neuronal activity in SNc and SNr and on striatal dopainine levels (S.A. V 1/2). Similarly, effects of "deep brain" stimulation and lesions of STN will be studied to assess the impact of these commonly used neurosurgical interventions on SNc and SNr activity, and on striatal DA. In the case of STN lesions, the density of glutamate and GABA receptors in SNc will also be determined (immunoautoradiography) as an inverse measure of the strength of glutamatergic and GABAergic inputs to SNc. These studies will provide insight into the role of the STN-SNc interaction under normal and parkinsonian conditions and will help to understand the mechanisms of action of neurosurgical treatments aimed at SIN in parkinsonian patients. -

Principal Investigator: York, Michele
Grant Number: 5K23NS041254-03
Title: Cognitive functioning following deep brain stimulation

Abstract: Dr. Michele York, under the mentorship of Dr. Harvey Levin, Director of Research of Baylor College of Medicine's (BCM) Physical Medicine and Rehabilitation Department and Professor of Psychiatry and Neurosurgery, and Dr. Robert Grossman, the Chairman of BCM's Neurosurgery Department, will more effectively evaluate the long-term cognitive effects of deep brain stimulation (DBS) for the treatment of Parkinson's disease (PD). The scientific objective of the proposed research plan is to more clearly understand the relationship between the frontostriatal neural circuitry affected by DBS and PD and cognitive functioning. The clinical objectives of the proposed research plan include improving upon the evaluation of outcome by improving cognitive diagnostic techniques, clarifying the clinical criteria for surgical selection, and incorporating analysis of post-operative magnetic resonance imaging (MRI) findings. To achieve these aims, Dr. York will compare the executive functioning of patients undergoing staged bilateral subthalamic (STN) and globus pallidus (GPI) DEIS to patients who receive the best medical management for the treatment of PD on verbal fluency measures administered under conditions of set shifting and attentional control and working memory measures, which are cognitive processes dependent on the functional integrity of frontostriatal circuitry. The relationship between DBS electrode placement and performance on these frontostriatal neuropsychological tasks will also be investigated. The objectives of the training program are to acquire practical and technical skills that will aid Dr. York in developing her career, specifically in the areas of neurosurgical interventions and neurological evaluations of PD, structural and functional neuroimaging, and the neuroscience of PD. This training will provide Dr. York with a better understanding of the cognitive deficits in PD and the mechanisms and consequences of emerging interventions for the treatment of this neurological disease. The training activities during the award period will consist of 3 major components: 1) Didactics through coursework, technical training seminars, rounds, and observation, 2) Supervisory Guidance through regularly scheduled meetings with mentors and an Advisory Committee, and 3) Instruction in the Responsible Conduct of Research. Dr. York will gain the necessary knowledge to attain her long-term career goal of working as an independent clinical researcher by acquiring the background and skills in neuroscience, neuroimaging, and grant preparation needed to write a ROI proposal to adapt these cognitive tasks to a functional imaging setting to further elucidate the neural mechanisms of PD and DBS. -